

1 Millennium Pharmaceuticals, Inc.**2 VELCADE™ (bortezomib) for Injection****3 Prescribing Information****4 DESCRIPTION**

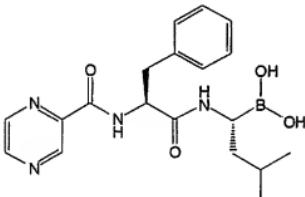
5
6 VELCADE™ (bortezomib) for Injection is an antineoplastic agent available for
7 intravenous injection (IV) use only. Each single dose vial contains 3.5 mg of bortezomib
8 as a sterile lyophilized powder. Inactive ingredient: 35 mg mannitol, USP.

9
10 Bortezomib is a modified dipeptidyl boronic acid. The product is provided as a mannitol
11 boronic ester which, in reconstituted form, consists of the mannitol ester in equilibrium
12 with its hydrolysis product, the monomeric boronic acid. The drug substance exists in its
13 cyclic anhydride form as a trimeric boroxine.

14
15 The chemical name for bortezomib, the monomeric boronic acid, is [(1R)-3-methyl-1-
16 [[(2S)-1-oxo-3-phenyl-2-[(pyrazinylcarbonyl)amino]propyl]amino]butyl]boronic acid.

17
18 Bortezomib has the following chemical structure:

19



20

21

22 The molecular weight is 384.24. The molecular formula is; C₁₉H₂₅BN₄O₄. The solubility
23 of bortezomib, as the monomeric boronic acid, in water is 3.3-3.8mg/mL in a pH range of
24 2-6.5.

25 CLINICAL PHARMACOLOGY**26 Mechanism of Action**

27 Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S
28 proteasome in mammalian cells. The 26S proteasome is a large protein complex that
29 degrades ubiquitinylated proteins. The ubiquitin-proteasome pathway plays an essential
30 role in regulating the intracellular concentration of specific proteins, thereby maintaining
31 homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted

32 proteolysis which can affect multiple signaling cascades within the cell. This disruption
33 of normal homeostatic mechanisms can lead to cell death. Experiments have
34 demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*.
35 Bortezomib causes a delay in tumor growth *in vivo* in non-clinical tumor models,
36 including multiple myeloma.
37

38 **Pharmacokinetics**

39 Following intravenous administration of 1.3 mg/m² dose, the median estimated maximum
40 plasma concentration of bortezomib was 509 ng/mL (range=109-1300 ng/mL) in eight
41 patients with multiple myeloma and creatinine clearance values ranging from 31-169
42 mL/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to
43 15 hours at doses ranging from 1.45 to 2.00 mg/m² in patients with advanced
44 malignancies. The pharmacokinetics of bortezomib as a single agent have not been fully
45 characterized at the recommended dose in multiple myeloma patients.
46

47 **Distribution**

48 The distribution volume of bortezomib as a single agent was not assessed at the
49 recommended dose in patients with multiple myeloma. The binding of bortezomib to
50 human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.
51

52 **Metabolism**

53 *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome
54 P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via
55 cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic
56 pathway is deboronation to form two deboronated metabolites that subsequently undergo
57 hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive
58 as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min
59 after dosing indicate that the plasma levels of metabolites are low compared to the parent
60 drug.
61

62 **Elimination**

63 The pathways of elimination of bortezomib have not been characterized in humans.
64

65 **Special Populations**

66
67 Age, Gender, and Race: The effects of age, gender, and race on the pharmacokinetics of
68 bortezomib have not been evaluated.
69
70 Hepatic Impairment: No pharmacokinetic studies were conducted with bortezomib in
71 patients with hepatic impairment (see PRECAUTIONS).
72
73

75 Renal Impairment: No pharmacokinetic studies were conducted with bortezomib in
76 patients with renal impairment. Clinical studies included patients with creatinine
77 clearances values ranging from 13.8 to 220 mL/min (see PRECAUTIONS).

78
79 Pediatric: There are no pharmacokinetic data in pediatric patients.
80

81 **Drug Interactions:**

82 No formal drug interaction studies have been conducted with bortezomib.

83 *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate of
84 cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2 (see PRECAUTIONS).

85
86 Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9,
87 2D6, and 3A4, with IC₅₀ values of > 30 µM (> 11.5 µg/mL). Bortezomib may inhibit
88 2C19 activity (IC₅₀=18 µM, 6.9 µg/mL) and increase exposure to drugs that are
89 substrates for this enzyme.

90
91 Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary
92 cultured human hepatocytes.
93

94 **CLINICAL STUDIES**

95 **Clinical Study in Relapsed and Refractory Multiple Myeloma**

96
97 The safety and efficacy of VELCADE were evaluated in an open-label, single-arm,
98 multicenter study of 202 patients who had received at least 2 prior therapies and
99 demonstrated disease progression on their most recent therapy. The median number of
100 prior therapies was six. Baseline patient and disease characteristics are summarized in
101 **Table 1.**

102
103 An IV bolus injection of VELCADE 1.3 mg/m²/dose was administered twice weekly for
104 2 weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of 8
105 treatment cycles. The study employed dose modifications for toxicity (see DOSAGE
106 AND ADMINISTRATION). Patients who experienced a response to VELCADE
107 treatment were allowed to continue VELCADE treatment in an extension study.
108

109 **Table 1: Summary of Patient Population and Disease Characteristics ***
110

| | N=202 |
|---|-------------|
| Patient Characteristics: | |
| Median Age in Years (Range) | 59 (34,84) |
| Gender: Male/Female | 60%/40% |
| Race: Caucasian/Black/Other | 81%/10%/8% |
| Karnofsky Performance Status Score \leq 70 | 20% |
| Hemoglobin <100 g/L | 44% |
| Platelet count <75 \times 10 ⁹ /L | 21% |
| Disease Characteristics: | |
| Type of myeloma (%): IgG/IgA/Light chain | 60%/24%/14% |
| Median β_2 -microglobulin (mg/L) | 3.5 |
| Median Creatinine Clearance (mL/min) | 73.9 |
| Abnormal Cytogenetics | 35% |
| Chromosome 13 Deletion | 15% |
| Median Duration of Multiple Myeloma Since Diagnosis in Years | 4.0 |
| Previous Therapy | |
| Any Prior Steroids, e.g., dexamethasone, VAD | 99% |
| Any Prior Alkylating Agents, e.g., MP, VBMCP | 92% |
| Any Prior Anthracyclines, e.g., VAD, mitoxantrone | 81% |
| Any Prior Thalidomide Therapy | 83% |
| Received at Least 2 of the Above | 98% |
| Received at Least 3 of the Above | 92% |
| Received All 4 of the Above | 66% |
| Any Prior Stem Cell Transplant /Other High-dose Therapy | 64% |
| Prior Experimental or Other Types of Therapy | 44% |

111 *Based on number of patients with baseline data available
112113 Responses to VELCADE alone are shown in **Table 2**. Response rates to VELCADE
114 alone were determined by an independent review committee (IRC) based on criteria
115 published by Blade and others¹. Complete response required < 5% plasma cells in the
116 marrow, 100% reduction in M protein, and a negative immunofixation test (IF-).
117 Response rates using the SWOG criteria are also shown. SWOG response required a \geq
118 75% reduction in serum myeloma protein and/or \geq 90% urine protein². A total of 188
119 patients were evaluated for response; 9 patients with nonmeasurable disease could not be
120 evaluated for response by the IRC. Five patients were excluded from the efficacy
121 analyses because they had minimal prior therapy.122
123 Ninety-eight percent of study patients received a starting dose of 1.3 mg/m². Twenty-
124 eight percent of these patients received a dose of 1.3 mg/m² throughout the study, while

125 33 % of patients who started at a dose of 1.3 mg/m² had to have their dose reduced during
126 the study. Sixty-three percent of patients had at least one dose held during the study. In
127 general, patients who had a confirmed CR received 2 additional cycles of VELCADE
128 treatment beyond confirmation. The mean number of cycles administered was six.

129
130 The median time to response was 38 days (range 30 to 127 days).
131 The median survival of all patients enrolled was 16 months (range <1 to 18+ months).

132 **Table 2: Summary of Disease Outcomes**

| Response Analyses (VELCADE monotherapy) | N=188 | N (%) | (95% CI) |
|---|-----------------|------------------|-----------------|
| Overall Response Rate (Blade) (CR + PR) | 52 (27.7%) | (21, 35) | |
| Complete Response(CR) ¹ | 5 (2.7%) | (1, 6) | |
| Partial Response(PR) ² | 47 (25%) | (19, 32) | |
| Clinical Remission (SWOG) ³ | 33 (17.6%) | (12, 24) | |
| Kaplan-Meier Estimated Median Duration of Response (95% CI) | 365 Days | (224, NE) | |

133 ¹ Complete response required 100% disappearance of the original monoclonal protein from blood and
134 urine on at least 2 determinations at least 6 weeks apart by immunofixation, and <5% plasma cells in the
135 bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.

136 ² Partial Response requires ≥ 50% reduction in serum myeloma protein and ≥ 90% reduction of urine
137 myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and
138 calcium.

139 ³ Clinical Remission (SWOG) required ≥75% reduction in serum myeloma protein and/or ≥ 90%
140 reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone
141 disease and calcium.

142
143 In this study, the response rate to VELCADE was independent of the number and types
144 of prior therapies. There was a decreased likelihood of response in patients with either
145 >50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen
146 in patients with chromosome 13 abnormalities.

147
148 A small dose-response study was performed in 54 patients with multiple myeloma
149 received a 1.0 mg/m²/dose or a 1.3 mg/m²/dose twice weekly for two out of three weeks.
150 A single complete response was seen at each dose, and there were overall (CR + PR)
151 response rates of 30% (8/27) at 1.0 mg/m² and 38% (10/26) at 1.3 mg/m².

INDICATIONS AND USAGE

VELCADE™ (bortezomib) for Injection is indicated for the treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy.

The effectiveness of VELCADE is based on response rates (see **CLINICAL STUDIES section**). There are no controlled trials demonstrating a clinical benefit, such as an improvement in survival.

CONTRAINDICATIONS

VELCADE is contraindicated in patients with hypersensitivity to bortezomib, boron or mannitol.

WARNINGS

VELCADE should be administered under the supervision of a physician experienced in the use of antineoplastic therapy.

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE.

Bortezomib was not teratogenic in nonclinical developmental toxicity studies in rats and rabbits at the highest dose tested (0.075 mg/kg; 0.5 mg/m² in the rat and 0.05 mg/kg; 0.6 mg/m² in the rabbit) when administered during organogenesis. These dosages are approximately half the clinical dose of 1.3 mg/m² based on body surface area.

Pregnant rabbits given bortezomib during organogenesis at a dose of 0.05mg/kg (0.6 mg/m²) experienced significant post-implantation loss and decreased number of live fetuses. Live fetuses from these litters also showed significant decreases in fetal weight. The dose is approximately 0.5 times the clinical dose of 1.3 mg/m² based on body surface area.

No placental transfer studies have been conducted with bortezomib. There are no adequate and well-controlled studies in pregnant women. If VELCADE is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

PRECAUTIONS

Peripheral Neuropathy: VELCADE treatment causes a peripheral neuropathy that is predominantly sensory, although cases of mixed sensori-motor neuropathy have also been reported. Patients with pre-existing symptoms (numbness, pain or a burning feeling in the feet or hands) and/or signs of peripheral neuropathy may experience worsening during treatment with VELCADE. Patients should be monitored for symptoms of

192 neuropathy, such as a burning sensation, hyperesthesia, hypesthesia, paresthesia,
193 discomfort or neuropathic pain. Patients experiencing new or worsening peripheral
194 neuropathy may require change in the dose and schedule of VELCADE (see DOSAGE
195 AND ADMINISTRATION). Limited follow-up data regarding the outcome of
196 peripheral neuropathy are available. Of the patients who experienced treatment emergent
197 neuropathy more than 70% had previously been treated with neurotoxic agents and more
198 than 80% of these patients had signs or symptoms of peripheral neuropathy at baseline
199 (Also see ADVERSE REACTIONS).

200 **Hypotension:** VELCADE treatment can cause orthostatic/postural hypotension in about
201 12% of patients. These events are observed throughout therapy. Caution should be used
202 when treating patients with history of syncope, patients receiving medications known to
203 be associated with hypotension, and patients who are dehydrated. Management of
204 orthostatic/postural hypotension may include adjustment of antihypertensive medications,
205 hydration, or administration of mineralocorticoids.

206 **Gastrointestinal Adverse Events:** VELCADE treatment can cause nausea, diarrhea,
207 constipation, and vomiting (see ADVERSE REACTIONS) sometimes requiring use of
208 antiemetics and antidiarrheals. Fluid and electrolyte replacement should be administered
209 to prevent dehydration.

211 **Thrombocytopenia:** Thrombocytopenia, which occurred in about 40% of patients
212 throughout therapy, was maximal at day 11 and usually recovered by the next cycle.
213 Complete blood counts including platelet counts should be frequently monitored
214 throughout treatment. Onset is most common in Cycles 1 and 2 but can continue
215 throughout therapy. There have been reports of gastrointestinal and intracerebral
216 hemorrhage in association with VELCADE induced thrombocytopenia. VELCADE
217 treatment may be temporarily discontinued if patients experience Grade 4
218 thrombocytopenia. VELCADE may be reinitiated at a reduced dose after resolution of
219 thrombocytopenia (see DOSAGE AND ADMINISTRATION and ADVERSE
220 REACTIONS).

221

222 **Patients with Hepatic Impairment:**

223 Bortezomib is metabolized by liver enzymes and bortezomib's clearance may decrease in
224 patients with hepatic impairment. These patients should be closely monitored for
225 toxicities when treated with VELCADE.

226 (see CLINICALPHARMACOLOGY/Pharmacokinetics-Special Populations)

227

228 **Patients with Renal Impairment:**

229 No clinical information is available on the use of VELCADE in patients with creatinine
230 clearance values less than 13 mL/min and patients on hemodialysis. These patients
231 should be closely monitored for toxicities when treated with VELCADE (see
232 CLINICAL PHARMACOLOGY/Pharmacokinetics-Special Populations).

233

234 **Animal Toxicity Findings:**

235

237 Cardiovascular toxicity

238
239 Studies in monkeys showed that administration of dosages approximately twice the
240 recommended clinical dose resulted in heart rate elevations, followed by profound
241 progressive hypotension, bradycardia, and death 12-14 hours post dose. Doses \geq 1.2
242 mg/m² induced dose proportional changes in cardiac parameters. Bortezomib has been
243 shown to distribute to most tissues in the body, including the myocardium. In a repeated
244 dosing toxicity study in the monkey, myocardial hemorrhage, inflammation, and necrosis
245 were also observed.

246 Chronic Administration

248

249 In animal studies at a dose and schedule similar to that recommended for patients (twice
250 weekly dosing for 2 weeks followed by 1 week rest) toxicities observed included severe
251 anemia and thrombocytopenia, gastrointestinal, neurological and lymphoid system
252 toxicities. Neurotoxic effects of bortezomib in animal studies included axonal swelling
253 and degeneration in peripheral nerves, dorsal spinal roots, and tracts of the spinal cord.
254 Additionally, multifocal hemorrhage and necrosis in the brain, eye, and heart were
255 observed.

256

257 **Information for Patients**

258 Physicians are advised to discuss the following with patients to whom VELCADE will be
259 administered.

260

261 *Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability:*
262 Since VELCADE may be associated with fatigue, dizziness, syncope, orthostatic/postural
263 hypotension, diplopia or blurred vision, patients should be cautious when operating
264 machinery, including automobiles.

265

266 *Pregnancy/Nursing:* Patients should be advised to use effective contraceptive measures to
267 prevent pregnancy and to avoid breast feeding during treatment with VELCADE.

268

269 *Dehydration/Hypotension:* Since patients receiving VELCADE therapy may experience
270 vomiting and/or diarrhea, patients should be advised regarding appropriate measures to
271 avoid dehydration. Patients should be instructed to seek medical advice if they
272 experience symptoms of dizziness, light headedness or fainting spells.

273

274 *Concomitant Medications:* Patients should be cautioned about the use of concomitant
275 medications that may be associated with peripheral neuropathy (such as amiodarone, anti-
276 virals, isoniazid, nitrofurantoin, or statins), or with a decrease in blood pressure.

277

278 *Peripheral Neuropathy:* Patients should be instructed to contact their physician if they
279 experience new or worsening symptoms of peripheral neuropathy (see PRECAUTIONS
280 and DOSAGE AND ADMINISTRATION).

281

282 Drug Interactions

283 No formal drug interaction studies have been conducted with VELCADE.

284

285 *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate for
286 cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Patients who are concomitantly
287 receiving VELCADE and drugs that are inhibitors or inducers of cytochrome P450 3A4
288 should be closely monitored for either toxicities or reduced efficacy (see **CLINICAL**
289 **PHARMACOLOGY/Pharmacokinetics-Drug Interactions**).

290

291 During clinical trials, hypoglycemia and hyperglycemia were reported in diabetic patients
292 receiving oral hypoglycemics. Patients on oral antidiabetic agents receiving VELCADE
293 treatment may require close monitoring of their blood glucose levels and adjustment of
294 the dose of their antidiabetic medication.

295

296 There have been several SAE reports since filing. These reports were submitted to the
297 IND. If the Agency feels this information is unnecessary, the language can be removed.

298 Drug Laboratory Test Interactions

299 None known.

300 Carcinogenesis, Mutagenesis, Impairment of Fertility

301 Carcinogenicity studies have not been conducted with bortezomib.

302

303 Bortezomib showed clastogenic activity (structural chromosomal aberrations) in the *in*
304 *vitro* chromosomal aberration assay using Chinese hamster ovary cells. Bortezomib was
305 not genotoxic when tested in the *in vitro* mutagenicity assay (Ames test) and *in vivo*
306 micronucleus assay in mice.

307

308 Fertility studies with bortezomib were not performed but evaluation of reproductive
309 tissues has been performed in the general toxicity studies. In the 6-month rat toxicity
310 study, degenerative effects in the ovary were observed at doses $\geq 0.3 \text{ mg/m}^2$ (one-fourth
311 of the recommended clinical dose), and degenerative changes in the testes occurred at 1.2 mg/m^2 .
312 VELCADE could have a potential effect on either male or female fertility.
313

314 Pregnancy Category D (see WARNINGS)

315

316 Nursing Mothers

317 It is not known whether bortezomib is excreted in human milk. Because many drugs are
318 excreted in human milk and because of the potential for serious adverse reactions in
319 nursing infants from VELCADE, women should be advised against breast feeding while
320 being treated with VELCADE.

321 Pediatric Use:

322 The safety and effectiveness of VELCADE in children has not been established.

323 **Geriatric Use:**

324 Of the 202 patients enrolled, 35% were 65 years of age or older. Nineteen percent (19%)
325 of patients aged 65 years or older experienced responses versus 32% in patients under the
326 age of 65. Across the 256 patients analyzed for safety, the incidence of Grade 3 or 4
327 events reported was 74%, 80%, and 85% for patients ≤ 50 years, 51 to 65 years, and > 65
328 years, respectively.

329 **ADVERSE REACTIONS**

331 The two studies described (see Clinical Studies) evaluated 228 patients with multiple
332 myeloma receiving VELCADE 1.3 mg/m²/dose twice weekly for 2 weeks followed by a
333 10-day rest period (21 day treatment cycle length) for a maximum of 8 treatment cycles.

334 The most commonly reported adverse events were asthenic conditions (including fatigue,
335 malaise and weakness) (65%), nausea (64%), diarrhea (51%), appetite decreased
336 (including anorexia) (43%), constipation (43%), thrombocytopenia (43%), peripheral
337 neuropathy (including peripheral sensory neuropathy and peripheral neuropathy
338 aggravated) (37%), pyrexia (36%), vomiting (36%), and anemia (32%).

339 Fourteen percent of patients experienced at least one episode of grade 4 toxicity, with the
340 most common toxicity being thrombocytopenia (3%) and neutropenia (3%).

341

342 **Serious Adverse Events (SAEs):** Serious Adverse Events are defined as any event,
343 regardless of causality that: results in death, is life-threatening, requires hospitalization or
344 prolongs a current hospitalization, results in a significant disability or is deemed to be an
345 important medical event. A total of 113 (50%) of the 228 patients experienced SAEs
346 during the studies. The most commonly reported SAEs included pyrexia (7%),
347 pneumonia (7%), diarrhea (6%), vomiting (5%), dehydration (5%), and nausea (4%).

348

349 Adverse events thought by the investigator to be drug-related and leading to
350 discontinuation occurred in 18% of patients. The reasons for discontinuation included
351 peripheral neuropathy (5%), thrombocytopenia (4%), diarrhea (2%), and fatigue (2%).

352

353 Two deaths were reported and considered by the investigator to be possibly related to
354 study drug: one case of cardiopulmonary arrest and one case of respiratory failure.

355

356 The most common adverse events are shown in Table 3. All adverse events occurring at
357 ≥ 10% are included. In the single arm studies conducted it is often not possible to
358 distinguish adverse events that are drug-caused and those that reflect the patient's
359 underlying disease. See discussion of specific adverse reactions following Table 3.

360 Table 3: Most Commonly Reported ($\geq 10\%$ Overall) Adverse Events (N=228)

| Adverse Event | All Patients (N = 228) [n (%)] | | |
|-----------------------------------|--------------------------------|----------------|----------------|
| | All Events | Grade 3 Events | Grade 4 Events |
| Asthenic conditions | 149 (65) | 42 (18) | 1 (<1) |
| Nausea | 145 (64) | 13 (6) | 0 |
| Diarrhea | 116 (51) | 16 (7) | 2 (<1) |
| Appetite decreased | 99 (43) | 6 (3) | 0 |
| Constipation | 97 (43) | 5 (2) | 0 |
| Thrombocytopenia | 97 (43) | 61 (27) | 7 (3) |
| Peripheral neuropathy | 84 (37) | 31 (14) | 0 |
| Pyrexia | 82 (36) | 9 (4) | 0 |
| Vomiting | 82 (36) | 16 (7) | 1 (<1) |
| Anemia | 74 (32) | 21 (9) | 0 |
| Headache | 63 (28) | 8 (4) | 0 |
| Insomnia | 62 (27) | 3 (1) | 0 |
| Arthralgia | 60 (26) | 11 (5) | 0 |
| Pain in limb | 59 (26) | 16 (7) | 0 |
| Edema | 58 (25) | 3 (1) | 0 |
| Neutropenia | 55 (24) | 30 (13) | 6 (3) |
| Paresthesia and dysesthesia | 53 (23) | 6 (3) | 0 |
| Dyspnea | 50 (22) | 7 (3) | 1 (<1) |
| Dizziness (excluding vertigo) | 48 (21) | 3 (1) | 0 |
| Rash | 47 (21) | 1 (<1) | 0 |
| Dehydration | 42 (18) | 15 (7) | 0 |
| Upper respiratory tract infection | 41 (18) | 0 | 0 |
| Cough | 39 (17) | 1 (<1) | 0 |
| Bone pain | 33 (14) | 5 (2) | 0 |
| Anxiety | 32 (14) | 0 | 0 |
| Myalgia | 32 (14) | 5 (2) | 0 |
| Back pain | 31 (14) | 9 (4) | 0 |
| Muscle cramps | 31 (14) | 1 (<1) | 0 |
| Dyspepsia | 30 (13) | 0 | 0 |
| Abdominal pain | 29 (13) | 5 (2) | 0 |
| Dysgeusia | 29 (13) | 1 (<1) | 0 |
| Hypotension | 27 (12) | 8 (4) | 0 |
| Rigors | 27 (12) | 1 (<1) | 0 |
| Herpes zoster | 26 (11) | 2 (<1) | 0 |
| Pruritus | 26 (11) | 0 | 0 |
| Vision blurred | 25 (11) | 1 (<1) | 0 |
| Pneumonia | 23 (10) | 12 (5) | 0 |

Asthenic conditions (fatigue, malaise, weakness)

361
362 Asthenia was reported in 65% of patients and was predominantly reported as Grade 1 or
363 2. The first onset of fatigue was most often reported during the 1st and 2nd cycles of
364 therapy. Asthenia was Grade 3 for 18% of patients. Two percent of patients
365 discontinued treatment due to fatigue.
366

Gastrointestinal Events

367 The majority of patients experienced gastrointestinal adverse events during the studies,
368 including nausea, diarrhea, constipation, and vomiting. Grade 3 or 4 gastrointestinal
369 events occurred in 21% of patients and were considered serious in 13% of patients.
370 Vomiting and diarrhea each were of Grade 3 severity in 7% of patients and were Grade 4
371 in <1%. Five percent of patients discontinued due to gastrointestinal events. Appetite
372 decreased (anorexia) was reported as an adverse event for 43% of patients. The
373 incidence of Grade 3 decreased appetite was 3%.
374

Thrombocytopenia

375 Thrombocytopenia was reported during treatment with VELCADE for 43% of patients.
376 The thrombocytopenia was characterized by a dose related decrease in platelet count
377 during the VELCADE dosing period (Days 1 to 11) with a return to baseline in platelet
378 count during the rest period (Days 12 to 21) in each treatment cycle. Thrombocytopenia
379 was Grade 3 or 4 in intensity for 27% and 3% respectively of patients. Four percent (4%)
380 of patients discontinued VELCADE treatment due to thrombocytopenia of any grade.
381

Peripheral Sensory Neuropathy

382 Events reported as peripheral neuropathy, peripheral sensory neuropathy, and peripheral
383 neuropathy aggravated occurred in 37% of patients. Peripheral neuropathy was Grade 3
384 for 14% of patients with no Grade 4 events. New onset or worsening of existing
385 neuropathy was noted throughout the cycles of treatment. Six percent (6%) of patients
386 discontinued VELCADE due to neuropathy. More than 80% of all study patients had
387 signs or symptoms of peripheral neuropathy at baseline evaluation. The incidence of
388 Grade 3 neuropathy was 5% (2 of 41 patients) in patients without baseline neuropathy.
389 Symptoms may improve or return to baseline in some patients upon discontinuation of
390 VELCADE. The complete time-course of this toxicity has not been fully characterized.
391

Pyrexia

392 Pyrexia (> 38°C) was reported as an adverse event for 36% of patients and was assessed
393 as Grade 3 in 4% of patients.
394

Neutropenia

395 Neutropenia occurred in 24% of patients and was grade 3 in 13% and grade 4 in 3%.
396 The incidence of febrile neutropenia was <1%.
397

406

Hypotension

408

409 Hypotension (including reports of orthostatic hypotension) was reported in 12% of
410 patients. Most events were Grade 1 or 2 in severity. Grade 3 hypotension occurred in
411 4% of patients; no patient experienced Grade 4 hypotension. Patients developing
412 orthostatic hypotension did not have evidence of orthostatic hypotension at study entry;
413 half had pre-existing hypertension and one third had evidence of peripheral neuropathy.
414 Doses of antihypertensive medications may need to be adjusted in patients receiving
415 VELCADE. Four percent of patients experienced hypotension, including orthostatic
416 hypotension, and had a concurrent syncopal event.

417

Serious Adverse Events from Clinical Studies

419

420 In approximately 580 patients, the following serious adverse events (not described above)
421 were reported, considered at least possibly related to study medication, in at least one
422 patient treated with VELCADE administered as monotherapy or in combination with
423 other chemotherapeutics. These studies were conducted in patients with hematological
424 malignancies and in solid tumors.

425

426 **Blood and lymphatic system disorders:** Disseminated intravascular coagulation

427

428 **Cardiac disorders:** Atrial fibrillation aggravated, atrial flutter, cardiac amyloidosis,
429 cardiac arrest, cardiac failure congestive, myocardial ischemia, myocardial infarction,
430 pericardial effusion, pulmonary edema, ventricular tachycardia

431

432 **Gastrointestinal disorders:** Ascites, dysphagia, fecal impaction, gastritis hemorrhagic,
433 gastrointestinal hemorrhage, hematemesis, ileus paralytic, large intestinal obstruction,
434 paralytic intestinal obstruction, small intestinal obstruction, large intestinal perforation,
435 stomatitis, melena, pancreatitis acute

436

437 **Hepatobiliary:** Hyperbilirubinemia, portal vein thrombosis

438

439 **Immune system disorders:** Anaphylactic reaction, drug hypersensitivity, immune
440 complex mediated hypersensitivity

441

442 **Infections and Infestations:** Bacteremia

443

444 **Injury, poisoning and procedural complications:** skeletal fracture, subdural hematoma

445

446 **Metabolism and nutrition disorders:** Hypocalcemia, hyperuricemia, hypokalemia,
447 hyponatremia, tumor lysis syndrome

448 **Nervous system:** Ataxia, coma, dizziness, dysarthria, dysautonomia, cranial palsy, grand
449 mal convulsion, hemorrhagic stroke, motor dysfunction, spinal cord compression,
450 transient ischemic attack

451

452 **Psychiatric:** Agitation, confusion, psychotic disorder, suicidal ideation

453

454 **Renal and urinary:** Calculus renal, bilateral hydronephrosis, bladder spasm, hematuria
455 urinary incontinence, urinary retention, renal failure, acute and chronic, glomerular
456 nephritis proliferative

457

458 **Respiratory, thoracic and mediastinal:** Acute respiratory distress syndrome,
459 atelectasis, chronic obstructive airways disease exacerbated, dysphagia, dyspnea, dyspnea
460 exertional, epistaxis, hemoptysis, hypoxia, lung infiltration, pleural effusion,
461 pneumonitis, respiratory distress, respiratory failure

462

463 **Vascular:** Cerebrovascular accident, deep venous thrombosis, peripheral embolism,
464 pulmonary embolism

465 **OVERDOSAGE**

466 Cardiovascular safety pharmacology studies in monkeys show that lethal IV doses are
467 associated with decreases in blood pressure, increases in heart rate, increases in
468 contractility, and ultimately terminal hypotension. In monkeys, doses of 3.0 mg/m^2 and
469 greater (approximately twice the recommended clinical dose) resulted in progressive
470 hypotension starting at 1 hour and progressing to death by 12 to 14 hours following drug
471 administration.

472

473 No cases of overdosage with VELCADE were reported during clinical trials. Single
474 doses of up to 2.0 mg/m^2 per week have been administered in adults. In the event of
475 overdosage, patient's vital signs should be monitored and appropriate supportive care
476 given to maintain blood pressure and body temperature (see **PRECAUTIONS AND**
477 **DOSAGE AND ADMINISTRATION**).

478

479 There is no known specific antidote for VELCADE overdosage.

480 **DOSAGE AND ADMINISTRATION**

481 The recommended dose of VELCADE is $1.3\text{ mg/m}^2/\text{dose}$ administered as a bolus
482 intravenous injection twice weekly for two weeks (days 1, 4, 8, and 11) followed by a 10-
483 day rest period (days 12-21) (see **CLINICAL STUDIES** section for a description of
484 **dose administration during the trials**).

485

486 This 3-week period is considered a treatment cycle. At least 72 hours should elapse
487 between consecutive doses of VELCADE.

488

489 **Dose Modification and Reinitiation of Therapy:**

491 VELCADE therapy should be withheld at the onset of any Grade 3 non-hematological or
492 Grade 4 hematological toxicities excluding neuropathy as discussed below (see
493 **PRECAUTIONS**). Once the symptoms of the toxicity have resolved, VELCADE
494 therapy may be reinitiated at a 25% reduced dose (1.3 mg/m²/dose reduced to 1.0
495 mg/m²/dose; 1.0 mg/m²/dose reduced to 0.7 mg/m²/dose). The following table contains
496 the recommended dose modification for the management of patients who experience
497 VELCADE-related neuropathic pain and/or peripheral sensory neuropathy (**Table 4**).
498 Patients with pre-existing severe neuropathy should be treated with VELCADE only after
499 careful risk/ benefit assessment.

500 **Table 4: Recommended Dose Modification for VELCADE-related neuropathic pain**
501 **and/or peripheral sensory neuropathy**

| Severity of Peripheral Neuropathy <i>Signs and Symptoms</i> | Modification of Dose and Regimen |
|--|---|
| Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function | No action |
| Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living) | Reduce VELCADE to 1.0 mg /m ² |
| Grade 2 with pain or Grade 3 (interfering with activities of daily living) | Withhold VELCADE therapy until toxicity resolves. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m ² and change treatment schedule to once per week. |
| Grade 4 (Permanent sensory loss that interferes with function) | Discontinue VELCADE |

502 NCI Common Toxicity Criteria website – <http://ctep.info.nih.gov/reporting/ctc.html>

503

504 **Administration Precautions:** VELCADE is an antineoplastic. Caution should be used
505 during handling and preparation. Proper aseptic technique should be used. Use of gloves
506 and other protective clothing to prevent skin contact is recommended. In clinical trials,
507 local skin irritation was reported in 5% of patients, but extravasation of VELCADE was
508 not associated with tissue damage.

509

510 **Reconstitution/Preparation for Intravenous Administration:** Prior to use, the contents
511 of each vial must be reconstituted with 3.5 mL of normal (0.9%) saline, Sodium Chloride
512 Injection, USP. The reconstituted product should be a clear and colorless solution.

513

514 Parenteral drug products should be inspected visually for particulate matter and
515 discoloration prior to administration whenever solution and container permit. If any
516 discoloration or particulate matter is observed, the reconstituted product should not be
517 used.

518

519 **Stability:** Unopened vials of VELCADE are stable until the date indicated on the
520 package when stored in the original package protected from light.

521

VELCADE contains no antimicrobial preservative. When reconstituted as directed, VELCADE may be stored at 25°C (77°F); excursions permitted from 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature]. Reconstituted VELCADE should be administered within eight hours of preparation. The reconstituted material may be stored in the original vial and/or the syringe prior to administration. The product may be stored for up to three hours in a syringe, however total storage time for the reconstituted material must not exceed eight hours when exposed to normal indoor lighting.

530 HOW SUPPLIED

VELCADE (*bortezomib*) for Injection is supplied as individually cartoned 10 mL vials containing 3.5 mg of *bortezomib* as a white to off-white cake or powder.

535 NDC 63020-049-01 3.5 mg single dose vial

537 STORAGE

539 Unopened vials may be stored at controlled room temperature 25° C (77° F); excursions
540 permitted from 15 to 30° C (59 to 86° F) [see USP Controlled Room Temperature].
541 Retain in original package to protect from light

543 Caution: Rx only

U.S. Patents: 5,780,454 6,083,903 6,297,317

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564

VELCADE™ (bortezomib) for Injection**Patient Information**

VELCADE is intended for use under the guidance and supervision of a health care professional. Please discuss the possibility of the following side effects with your doctor:

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability: VELCADE may be associated with fatigue, dizziness, light-headedness, fainting or blurred vision. Please exercise caution or avoid operating machinery, including automobiles, following use of VELCADE.

Pregnancy/Nursing: Please use effective contraceptive measures to prevent pregnancy and avoid breast feeding during treatment with VELCADE.

Dehydration/Hypotension: Following the use of VELCADE therapy, you may experience vomiting and/or diarrhea. Drink plenty of fluids. Speak with your doctor if these symptoms occur and what you should do to control or manage these symptoms.

If you experience symptoms of dizziness or light-headedness, consult a healthcare professional. Seek immediate medical attention if you experience fainting spells.

Concomitant Medications: Please speak with your doctor about any other medication you are currently taking. Your doctor will want to be aware of any other medications.

Peripheral Neuropathy: Contact your doctor if you experience new or worsening symptoms of peripheral neuropathy, such as numbness, pain, or a burning feeling in the feet or hands.